

IN THE CLAIMS

Please AMEND the claims as follows:

Claims 1-82. (Canceled)

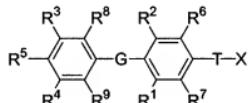
Claim 83. (Withdrawn): A method of preventing or treating a metabolic disease comprising administering to an animal a pharmaceutically effective amount of a phosphonic acid-containing compound of Claim 232, a pharmaceutically acceptable salt thereof, or prodrugs thereof or pharmaceutically acceptable salts of said prodrugs, wherein said phosphonic acid containing compound binds to a thyroid receptor.

Claims 84-99. (Canceled)

Claim 100. (Withdrawn): A method of activating a thyroid receptor in an animal by administering a phosphonic acid-containing-compound of Claim 232, wherein said activation results in the 50% or greater increase in the mRNA expression of a gene selected from the group consisting of LDL receptor, ACC, FAS, spot-14, CPT-1, CYP7A, apo AI, and mGPDH.

Claims 101-231. (Canceled)

Claim 232. (Currently Amended): A compound of Formula VIII:



wherein:

G is selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂-, -Se-, -CH₂-, -CF₂-, -CHF-, -C(O)-, -CH(OH)-, -CH(C₁-C₄ alkyl)-, -CH(C₁-C₄ alkoxy)-, -C(=CH₂)-, -NH-, and -N(C₁-C₄ alkyl)-;

T is selected from the group consisting of -(CR^a)_k-, -CR^b-CR^b-(CR^a)_n-, -(CR^a)_n-CR^b=CR^b-, -(CR^a)_n-CR^b=CR^b-(CR^a)_n-, -O(CR^b)_n(CR^a)_m-, -S(CR^b)_n(CR^a)_m-, N(R^c)(CR^b)_n(CR^a)_m-, N(R^b)C(O)(CR^a)_n-, -(CR^a)_nCH(NR^bR^c)-, -C(O)(CR^a)_m-, -(CR^a)_mC(O)-, -(CR^a)_nC(O)(CR^a)_n-, -(CR^a)_nC(O)(CR^a)_n-, and -C(O)NH(CR^b)_n(CR^a)_p-;

k is an integer from 1-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted -C₁-C₄ alkyl, halogen, -OH, optionally substituted -O-C₁-C₄ alkyl, -OCF₃, optionally substituted -S-C₁-C₄ alkyl, -NR^bR^c, optionally substituted -C₂-C₄ alkenyl, and optionally substituted -C₂-C₄ alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted -C₁-C₄ alkyl;

Each R^c is independently selected from the group consisting of hydrogen and optionally substituted -C₁-C₄ alkyl, optionally substituted -C(O)-C₁-C₄ alkyl, and -C(O)H;

R¹, and R² are each independently selected from the group consisting of halogen, optionally substituted -C₁-C₄ alkyl, optionally substituted -S-C₁-C₃ alkyl, optionally substituted -C₂-C₄ alkenyl, optionally substituted -C₂-C₄ alkynyl, -CF₃, -OCF₃, optionally substituted-O-C₁-C₃ alkyl, and cyano;

R⁶, R⁷, R⁸, and R⁹ are each independently selected from the group consisting of are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C₁-C₄ alkyl, optionally substituted -S-C₁-C₃ alkyl, optionally substituted -C₂-C₄ alkenyl, optionally substituted -C₂-C₄ alkynyl, -CF₃, -OCF₃, optionally substituted-O-C₁-C₃ alkyl, and cyano;

or R⁶ and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms including 0 to 2 heteroatoms independently selected from —NRⁱ—, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by -(CR^a)₂- or -C(O)- bonded to a ring carbon or a ring nitrogen;

Rⁱ is selected from the group consisting of hydrogen, -C(O)C₁-C₄ alkyl, -C₁-C₄ alkyl, and -C₁-C₄-aryl;

R³ and R⁴ are independently is selected from the group consisting of hydrogen, halogen, -CF₃, -OCF₃, cyano, optionally substituted -C₁-C₁₂ alkyl, optionally substituted -C₂-C₁₂ alkenyl,

optionally substituted $-C_2-C_{12}$ alkynyl, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

R^4 is selected from the group consisting of hydrogen, halogen, CF_3 , OCF_3 , cyano, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $(CR^a)_2$ naryl, optionally substituted $(CR^a)_2$ eycloalkyl, optionally substituted $(CR^a)_2$ heterocycloalkyl, $-OR^d$, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $(CR^b)_2$ naryl, optionally substituted $(CR^b)_2$ cycloalkyl, optionally substituted $(CR^b)_2$ heterocycloalkyl, and $-C(O)NR^fR^g$;

Each R^e is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $(CR^a)_2$ naryl, optionally substituted $(CR^a)_2$ cycloalkyl, and optionally substituted $(CR^a)_2$ heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $(CR^b)_2$ naryl, optionally substituted $(CR^b)_2$ cycloalkyl, and optionally substituted $(CR^b)_2$ heterocycloalkyl, and R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group consisting of O, NR^c , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted $-C_1-C_4$ alkyl, $-OR^b$, oxo, cyano, $-CF_3$, optionally substituted phenyl, and $-C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $(CR^b)_2$ naryl, optionally substituted $(CR^b)_2$ cycloalkyl, and optionally substituted $(CR^b)_2$ heterocycloalkyl;

R^5 is selected from the group consisting of -OH, optionally substituted -OC₁-C₆ alkyl, OC(O)R^c, -OC(O)OR^b, -F, -NHC(O)R^c, -NHS(=O)R^c, -NHS(=O)₂R^c, -NHC(=S)NH(R^b), and -NHC(O)NH(R^b);

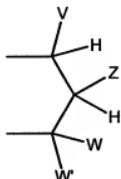
X is P(O)YR¹¹YR¹¹;

Y and Y' are each independently selected from the group consisting of -O-, and -NR^v-; when Y and Y' are -O-, R¹¹ attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH₂-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R^y, -C(R²)₂OC(O)R^y, -C(R²)₂-O-C(O)OR^y, -C(R²)₂OC(O)SR^y, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-alkylhydroxy;

when Y and Y' are -NR^v-, then R¹¹ attached to -NR^v- is independently selected from the group consisting of -H, -[C(R²)₂]_q-COOR^y, -C(R²)₂COOR^y, -[C(R²)₂]_q-C(O)SR^y, and -cycloalkylene-COOR^y;

when Y is -O- and Y' is NR^v, then R¹¹ attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH₂-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R^y, -C(R²)₂OC(O)R^y, -C(R²)₂-O-C(O)OR^y, -C(R²)₂OC(O)SR^y, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-alkylhydroxy; and R¹¹ attached to -NR^v- is independently selected from the group consisting of H, -[C(R²)₂]_q-COOR^y, -C(R²)₂COOR^y, -[C(R²)₂]_q-C(O)SR^y, and -cycloalkylene-COOR^y;

or when Y and Y' are independently selected from -O- and -NR^v-, then together R¹¹ and R¹¹ are -alkyl-S-S-alkyl- to form a cyclic group, or together R¹¹ and R¹¹ are the group:



wherein:

V, W, and W' are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted 1-alkenyl, and optionally substituted 1-alkynyl;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, substituted with hydroxy, acyloxy, alkylthiocarbonyloxy, alkoxy carbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

or together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy carbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

or together Z and W are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

or together W and W' are connected via an additional 2-5 atoms to form a cyclic group, wherein 0-2 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR^zOH, -CHR^zOC(O)R^y, -CHR^zOC(S)R^y, -CHR^zOC(S)OR^y, -CHR^zOC(O)SR^y, -CHR^zOC(O)R^y, -OR^z, -SR^z, -CHR^zN₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR^z)OH, -CH(C≡CR^z)OH, -R^z, -NR^z₂, -OCOR^y, -OCO₂R^y, -SCOR^y, -SCO₂R^y, -NHCOR^z, -NHCO₂R^y, -CH₂NHaryl, -(CH₂)_qOR^z, and -(CH₂)_qSR^z;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cyclic alkyl group;

Each R^y is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxyacryloxyalkyl, and lower acyl;

with the provisos that:

a) when G is -O-, T is -CH₂-, R¹ and R² are each bromo, R³ is *iso*-propyl, R⁴ is hydrogen, and R⁵ is -OH, then X is not P(O)(OH)₂ or P(O)(OCH₂CH₃)₂;

b) V, Z, W, W' are not all -H; and

c) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or heterocycloalkyl;

d) when G is -O-, T is -(CH₂)₁₋₄-, R¹ and R² are independently halogen, alkyl of 1 to 3 carbons, and cycloalkyl of 3 to 5 carbons, R³ is alkyl of 1 to 6 carbons, R⁴ is hydrogen, and R⁵ is -OH, then X is not -P(O)(OH)₂ or -P(O)(O lower alkyl)₂; and

e) when G is -O-, R⁵ is -NHC(O)R^e, -NHS(=O)₁₋₂R^e, -NHC(S)NH(R^b), or -NHC(O)NH(R^b), T is -(CH₂)_m, -CH=CH-, -O(CH₂)₁₋₂-, or -NH(CH₂)₁₋₂-, then X is not -P(O)(OH)₂ or -P(O)(OH)NH₂;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

Claims 233-240. (Canceled)

Claim 241. (Previously Presented): A pharmaceutical compositions comprising a pharmaceutically acceptable amount of a compound of any one of claims 232 or 242-255.

Claim 242. (Previously Presented): The compounds of claim 232, wherein: G is selected from the group consisting of -O- and -CH₂; R⁵ is selected from the group consisting of -OH or -F; and R⁶ and T may not be taken together along with the carbons they are attached to form a ring.

Claim 243. (Previously Presented): The compounds of claim 232, wherein: G is selected from the group consisting of -O- and -CH₂; R¹ and R² are each independently selected

from the group consisting of halogen, optionally substituted -C₁-C₄ alkyl, and cyano; R⁵ is selected from the group consisting of -OH or -F; and R⁶, R⁷, R⁸, and R⁹ are hydrogen.

Claim 244. (Previously Presented): The compounds of claim 232, wherein:

G is selected from the group consisting of -O- and -CH₂-;

R¹ and R² are each independently selected from the group consisting of halogen, optionally substituted -C₁-C₄ alkyl, and cyano;

R³ is selected from the group consisting of optionally substituted -C₁-C₁₂ alkyl, optionally substituted -C₂-C₁₂ alkenyl, and optionally substituted -C₂-C₁₂ alkynyl,

R⁴ is hydrogen;

R⁵ is selected from the group consisting of -OH or -F; and

R⁶, R⁷, R⁸, and R⁹ are hydrogen.

Claim 245 (Previously Presented): The compounds of claim 232, wherein

G is selected from the group consisting of -O- and -CH₂-;

T is selected from the group consisting of -(CR^a₂)_k, -O(CR^b₂)(CR^a₂)_n, -C(O)(CR^a₂)_m, -(CR^a₂)_mC(O)-, -(CR^a₂)C(O)(CR^a₂)_n, -(CR^a₂)_nC(O)(CR^a₂)_m- and -C(O)NH(CR^b₂)(CR^a₂)_p-;

R¹ and R² are each independently selected from the group consisting of halogen, optionally substituted -C₁-C₄ alkyl, and cyano;

R⁶, R⁷, R⁸, and R⁹ are hydrogen;

R³ is an optionally substituted -C₁-C₁₂ alkyl;

R⁴ is hydrogen;

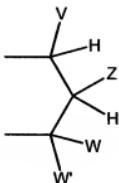
R⁵ is selected from the group consisting of -OH or -F;

Y and Y' are each independently selected from the group consisting of -O-, and -NR^v-; when Y and Y' are -O-, R¹¹ attached to -O- is independently selected from the group consisting of -H, -C(R^z)₂-OC(O)R^y, and -C(R^z)₂-O-C(O)OR^y;

when Y and Y' are -NR^v-, then R¹¹ attached to -NR^v- is independently selected from the group consisting of -H, -C(R^x)₂COOR^y, and -cycloalkylene-COOR^y;

when Y is -O- and Y' is NR^v, then R¹¹ attached to -O- is independently selected from the group consisting of -H, and optionally substituted aryl; and R¹¹ attached to -NR^v- is independently selected from the group consisting of H, -C(R^x)₂COOR^y, and -cycloalkylene-COOR^y;

or when Y and Y' are independently selected from -O- and -NR^Y-, then together R¹¹ and R¹¹ are the group:



wherein:

V is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

W, W' and Z are H.

Claim 246. (Previously Presented) A compound of claim 232, wherein

G is -CH₂;

T is selected from the group consisting of CH₂, CH₂CH₂, OCH₂, C(O)CH₂, and CH₂C(O);

R¹ and R² are each independently selected from the group consisting of halogen, optionally substituted -C₁-C₄ alkyl, and cyano;

R⁶, R⁷, R⁸, and R⁹ are hydrogen;

R³ is an optionally substituted -C₁-C₁₂ alkyl;

R⁴ is hydrogen;

R⁵ is selected from the group consisting of -OH or -F;

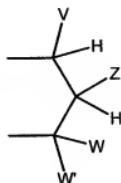
Y and Y' are each independently selected from the group consisting of -O-, and -NR^Y-; when Y and Y' are -O-, R¹¹ attached to -O- is independently selected from the group consisting of -H, -C(R²)₂-OC(O)R^Y, and -C(R²)₂-O-C(O)OR^Y;

when Y and Y' are -NR^Y, then R¹¹ attached to -NR^Y- is independently selected from the group consisting of -H, -C(R³)₂COOR^Y, and -cycloalkylene-COOR^Y;

when Y is -O- and Y' is NR^Y, then R¹¹ attached to -O- is independently selected from the group consisting of -H, and optionally substituted aryl; and R¹¹ attached to -NR^Y- is

independently selected from the group consisting of H, $-C(R^8)_2COOR^9$, and $-cycloalkylene-COOR^9$;

or when Y and Y' are independently selected from $-O-$ and $-NR^Y-$, then together R^{11} and R^{11} are the group:



wherein:

V is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

W, W' and Z are H.

Claim 247. (Previously Presented) The compounds of claim 232 wherein: G is $-CH_2-$; R^5 is selected from the group consisting of $-OH$ or $-F$; and R^6 and T may not be taken together along with the carbons they are attached to form a ring.

Claim 248. (Previously Presented): The compounds of claim 232, wherein: G is $-CH_2-$; R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted $-C_1-C_4$ alkyl, and cyano; R^5 is selected from the group consisting of $-OH$ or $-F$; and R^6 , R^7 , R^8 , and R^9 are hydrogen.

Claim 249. (Previously Presented): The compounds of claim 232, wherein:

G is $-CH_2-$;

R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted $-C_1-C_4$ alkyl, and cyano;

R^3 is independently selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, and optionally substituted $-C_2-C_{12}$ alkynyl;

R^4 is hydrogen;

R^5 is selected from the group consisting of $-OH$ or $-F$; and

R^6 , R^7 , R^8 , and R^9 are hydrogen.

Claim 250. (Previously Presented): The compounds of claim 232, wherein

G is $-CH_2-$;

T is selected from the group consisting of $-(CR^a_2)_k$, $-O(CR^b_2)(CR^a_2)_n$, $-C(O)(CR^a_2)_m$, $-(CR^a_2)_mC(O)$, $-(CR^a_2)C(O)(CR^a_2)_n$, $-(CR^a_2)_nC(O)(CR^a_2)$ and $-C(O)NH(CR^b_2)(CR^a_2)_p$;

R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted $-C_1-C_4$ alkyl, and cyano;

R^6 , R^7 , R^8 , and R^9 are hydrogen;

R^3 is an optionally substituted $-C_1-C_{12}$ alkyl;

R^4 is hydrogen;

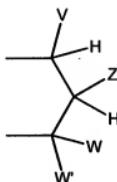
R^5 is selected from the group consisting of $-OH$ or $-F$;

Y and Y' are each independently selected from the group consisting of $-O-$, and $-NR^y-$; when Y and Y' are $-O-$, R^{11} attached to $-O-$ is independently selected from the group consisting of $-H$, $-C(R^z)_2-OC(O)R^y$, and $-C(R^z)_2-O-C(O)OR^y$;

when Y and Y' are $-NR^y-$, then R^{11} attached to $-NR^y-$ is independently selected from the group consisting of $-H$, $-C(R^x)_2COOR^y$, and $-cycloalkylene-COOR^y$;

when Y is $-O-$ and Y' is NR^y , then R^{11} attached to $-O-$ is independently selected from the group consisting of $-H$, and optionally substituted aryl; and R^{11} attached to $-NR^y-$ is independently selected from the group consisting of H , $-C(R^x)_2COOR^y$, and $-cycloalkylene-COOR^y$;

or when Y and Y' are independently selected from $-O-$ and $-NR^y-$, then together R^{11} and R^{11} are the group:

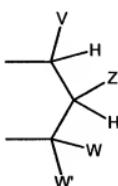
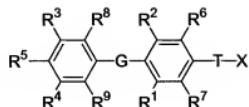


wherein:

V is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

W, W' and Z are H.

Claim 251. (Previously Presented) A compound of Formula VIII:



wherein:

V is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

W, W' and Z are H;

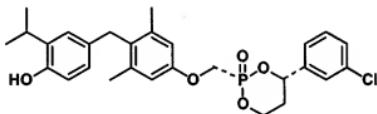
or a pharmaceutically acceptable salt thereof.

Claim 252. (Previously Presented) The compounds of claim 251, wherein R¹ and R² are each -CH₃.

Claim 253. (Previously Presented) The compounds of claim 251, wherein V is phenyl substituted by one or two groups selected from fluoro and chloro.

Claim 254. (Previously Presented) The compounds of claim 251, wherein V is 3-chlorophenyl.

Claim 255. (Previously Presented) A compound having a structure:



or a pharmaceutically acceptable salt thereof.